THE CENTRAL NERVOUS SYSTEM AND ANESTHESIA

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Since the introduction of anesthesia the fact has been recognized that the prime focus of anesthetic action is on the central nervous system. In recent years important advances have been made in understanding the mechanisms involved in anesthesia. I wish to present what appears to be one of the most significant of these advances and to attempt to correlate this with other facts, and finally to point out a few of the unanswered questions regarding the mechanism of anesthesia.

In a recent study, French, Verzeano and Magoun (1) have shown quite clearly how certain aspects of the anesthetic state are intimately related to the function of the so-called reticular activating system of the brain stem. For a better understanding of this achievement and its significance, it will be of advantage to discuss briefly the activities of the brain stem reticular formation in general. The investigations on which this knowledge is founded have been carried out chiefly by Magoun and his school (2, 3).

The first major aspect of the function of this structure to be studied was its caudal influences on motor activity of the spinal cord. When the bulbar part of the formation is stimulated, spinal reflexes are suppressed. For example, the intensity of the knee jerk is reduced or the threshold for its elicitation is raised. This effect is best elicited by stimulation of the ventromedian part of the formation. It influences not only local cord reflexes but cortical motor responses as well. If stimulation is carried out more anteriorly, the opposite effect is seen, a facilitation of spinal cord activity. The facilitatory formation covers a wider area and extends anteriorly as far as the diencephalon. It should not be assumed that these structures are autonomous. Indeed, it has been shown that the cerebral cortex and the cerebellum have functional connections with the reticular formation (4, 5), and that the facilitation and suppression of reflexes caused by stimulating these structures are mediated through the reticular formation. Suggestions have been made on the relation of the suppressor and facilitatory effects to spastic and dyskinetic states (6),

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and it may well be that the reticular formation is involved in the mechanism of such clinical conditions. The evidence indicates that increased motor activity seen in decerebrate rigidity is brought about to a considerable extent at least by uncontrolled activity of the facilitatory area (7, 8). Certainly, the reticular formation plays a central role in the normal regulation of motor activity.

Another activity of the nervous system that is of prime interest to the anesthesiologist is consciousness. To avoid the many pitfalls in characterizing and analyzing this state, I shall consider one aspect of it which is more amenable to objective investigation, that is, wakefulness as opposed to sleep. Certainly, all are agreed that wakefulness is a function of the higher nervous structures. It is equally true, however, that influences arising from and transmitted by other parts of the nervous system play an essential role in the maintenance of this state. For many years it has been recognized that sensory inputs to the cerebral cortex are an integral part of the mechanism for sustaining consciousness. The common observation that sleep is more easily induced in the absence of extraneous stimuli while wakefulness ensues upon such stimuli is strong evidence for this view.

The electro-encephalogram is closely correlated with the state of consciousness so that the pattern obtained may be used as an index of the level of wakefulness. In the fully alert individual, the predominant pattern is one of fast, low amplitude waves, activity manifested by different areas of cortex being generally asynchronous. With relaxation, the so-called alpha rhythm appears. This consists of higher amplitude, 10 to 15 per second waves which begin to be synchronous. With the advent of drowsiness and the attainment of sleep, large, slower \( \frac{1}{2} \) to 3 per second waves occur, with spindle bursts among them. This picture is reversed with waking, either spontaneous or brought about by some external stimulus.

It has been shown that stimulation of the reticular formation, within an area generally co-extant with that involved in spinal motor activity, produces a change in the electro-encephalogram of a drowsing animal identical to that seen in the waking state (3). The slow waves disappear and the pattern becomes desynchronized; the electro-encephalogram is said to be "activated." Conversely, destruction of this area abolishes the activation. Moreover, the animal becomes somnolent, is aroused with difficulty and lapses back into sleep, apparently unable to maintain the waking state. Thus it is evident that the ascending reticular activating system is of prime importance in maintenance of the waking state, in its behavioral aspects as well as in the electro-encephalographic correlate.

Further investigation has shown that the classical sensory pathways coursing in the brain stem give off collaterals to the reticular formation (9). Each sensory modality so far tested participates in a sort of pooling of impulses here. Apparently transmission of these
impulses through the reticular formation involves a number of synapses, for there is a significant delay before the impulses arrive at the cerebral cortex. The area in which these relays occur is co-extant with the activating system. Thus, a dual path exists for sensory inputs to the cerebral cortex. Insofar as the effects of sensory stimuli on wakefulness are concerned, those associated with the conduction of impulses anteriorly through the brain stem itself are depressed. It appears from this study that the activity of the reticular formation, in terms of its relation to sensory impulses to the cortex and its activation of the electro-encephalogram, is indeed integrally correlated with the effect of anesthesia on consciousness. French and his co-workers suggest that this brain stem structure is more readily depressed because of the large number of relays involved in transmission of impulses through it. It is to be hoped that these studies will be continued as they represent a most promising approach to a fuller understanding of anesthesia. The analogous observation of the effect of anesthetic agents on the reticular formation with respect to its influence on spinal reflexes has not been reported; such an investigation is surely indicated.

On the basis of these new facts as well as previous knowledge of the nervous system, the behavioral characteristics of anesthesia in terms of alteration of neural mechanism may now be considered. For this purpose, it is most convenient to follow Guedel's (11) scheme of classifying anesthetic action according to clinical stages; some modifications of this scheme proposed by Laycock (12) will be helpful in the present discussion.

Stage 1 is characterized by analgesia and disorientation. The meager information available (13) indicates that analgesia does not exist in any "pure" form but is associated at any level with some degree of impairment of mental ability. Moreover, changes in affect and judgment occur. It may also be noted that the analgesia, at least during the early stages, seems to be primarily due to an effect on the attitude toward pain as well as on the amelioration of its intensity (13). The sum of these effects is reminiscent of the results of frontal lobotomy (14) and suggests that part of this initial action of the anesthetic is at the level of the cerebral cortex with perhaps a preponderance on the frontal lobes. One must also consider, on the basis of what has just been said, that alteration in quality or intensity of sensation seen in this stage may to a considerable extent be the result of the effects of the agent on the reticular formation. First, the depression of transmission of ascending impulses through the brain stem may be responsible both for the observed change of pain threshold (13) and for the change in so-called pain reaction. Second, the alteration in electro-encephalographic activation may conceivably be related to the alteration in mental function which in turn reflects a change in cerebral cortical activity.
The second stage has been characterized by Guedel (11) as the stage of delirium but, although this is a characteristic event during induction with certain agents, it is largely absent with others. Laycock (12) has suggested the title "unconsciousness with reflex activity" for stage 2 and this denotes well the major clinical characteristics. Unconsciousness may result from an increase in the functional depression that has commenced in stage 1; that is, the demonstrated decrease in transmission of sensory impulses by way of the reticular formation becomes of still greater significance, while inactivation of the cortex goes on apace. When delirium, excitement or the "uninhibited reaction" takes place, it may be conceived of as the result of depression of inhibitory influences arising in the cortex and associated structures of the anterior brain stem. The excitement and fighting are strongly reminiscent of "sham rage" seen in the decorticate animal in which inhibition of the function of the hypothalamus in emotional expression is lacking. Under some circumstances, such as in anesthesia accompanying inhalation of 30 per cent carbon dioxide, a picture closely resembling decerebrate rigidity may be seen (15). Thus, there are manifestations in stage 2 of a progressive depression of neural function from the cerebral cortex downward. The presumption is justified that much of the behavioral change seen in this stage may be related to the demonstrated effect of anesthesia on the reticular function. This applies particularly to the advent of unconsciousness, wherein sensory inputs to the cortex are further diminished and the activating function of the reticular formation is depressed.

Turning next to the third or "surgical" stage, one may, with Laycock, characterize the state of the patient as "unconsciousness with reflex depression." The excitatory manifestations of the previous stage are absent. There is no fighting; the reflexes are not exaggerated, but instead become progressively depressed, and the musculature loses its tone. It is as if the decerebrate rigidity had been abolished by a section below the vestibular nuclei, or reduced by destruction of the facilitatory area of the reticular formation. An inhibition of activity through the direct action of the anesthetic on the spinal cord may supplement the waning of facilitation by brain stem mechanisms. The sum of such effects would result in the clinical picture seen in stage 3. The depth of unconsciousness and the diminution in reflex activity and muscle tone increase through the several clinical planes as the anesthetic agent manifests its action more profoundly. Action at any one site increases and a progressively increasing number of functional areas are involved.

Finally, paralysis of the respiratory center occurs, characterizing the onset of stage 4. It is evident that the respiratory mechanism is more resistant to anesthetic action than are the several other brain stem mechanisms already considered. Detailed reports of resistance to anesthesia of the respiratory and other medullary centers as con-
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trated to that of the spinal cord have not been found. Certainly, however, the respiratory mechanism is clinically the last to be completely disrupted.

From the previous consideration one fact emerges, that the phenomenon of clinical anesthesia is amenable to analysis on the basis of known physiology of the central nervous system. This is not to say, however, that the proposed scheme is complete or even in many of its aspects accurate. In most respects, it is admittedly speculative. To the extent that this scheme is based on analogies between the anesthetic state and the results of physiological experiments, it suffers from the limitations of any analogy. It is not sufficient merely to note that a particular characteristic of the anesthetic state may be explicable on the basis of certain neural changes. Such changes must actually be demonstrated to occur as has been done in the case of the ascending reticular activating system. The field of investigation here is wide open.

With this reservation in mind, it can be concluded that the progression of events in anesthesia represents a graded effect of the agent on neural structures, usually from the highest ones downward. The levels of the hierarchy of motor mechanisms, and those involved in consciousness as well, differ in their sensitivity to anesthetics. Obviously, the cellular aggregates vary in their ability to withstand the environmental change. Possible explanations for this situation may be considered next.

The order in which functional areas are depressed in anesthesia parallels quite closely the sensitivity of these structures to anoxia (16). In terms of both depression of function and irreversible damage induced by ischemia, the cerebral cortex is most sensitive, followed by the brain stem, the autonomic centers of the medulla and finally the spinal cord. It would be an attractive hypothesis to consider that the selective actions of anesthetics were the result of gross anoxia and that the selectivity was a matter of the specific sensitivities to this change. Unfortunately for this view, however, the available evidence is not supportive.

In the first place, as those familiar with anesthesia are aware, full anesthetization may occur in the presence of complete oxygenation of the blood. Although evidence exists indicating a decrease in cerebral blood flow with some anesthetics (17), this apparently is not sufficient to reduce below adequate levels the amount of oxygen available. The factor of anoxic or ischemic anoxia of the central nervous system in anesthesia may thus be ruled out. As indirect confirmation of this proposition stands the fact that anoxia sufficient to produce unconsciousness of the depth and duration of clinical anesthesia would result in irreversible damage to the brain.

Although adequate oxygen is available to the nervous system during anesthesia, a change may occur in the utilization of oxygen.
During both barbiturate and ether anesthesia a decrease in the anteriovenous oxygen difference of cerebral blood is observed (17). This indicates that the tissue loses part of its ability properly to take up or utilize oxygen, and that to some extent its metabolism is depressed. On the other hand, however, synaptic transmission may be depressed significantly without detectable change in oxygen consumption (18). A comparison here is dangerous, for in the former case the intact functioning brain was tested, while in the latter it was an isolated ganglion.

Studies on the respiration of isolated nervous tissue have thrown some light on cellular mechanisms that may be altered by anesthetic agents. Several excellent reviews (19–23) relate the many investigations carried out along these lines. For our purpose it will suffice to point out a few of the major findings. First, it has been shown that anesthetics may depress in vitro respiration at concentrations in the range found in clinical anesthesia, although this is not a uniform finding. Within certain groups of anesthetics, the inhibition of oxygen uptake is roughly parallel to the narcotic potency (23). Moreover, specific metabolic effects of the anesthetics have been studied and modes of interference with normal cellular activity have been elucidated. The difficulty has been in the correlation of the findings on isolated or minced tissue with the gross behavioral effects. In some instances, anesthetic agents do not follow the above pattern and fail to show significant effects on cellular respiration at clinically effective concentrations (24). Such results might indicate an action which is undetectable by the methods used but which is adequate to produce the clinical effect. The possibility exists, too, that only a relatively small number of cells need be affected to produce the over-all response to the anesthetic agent. More important even is the possibility that the anesthetic agent has little significant effect on resting metabolism, but somehow interferes with specific nervous function. This apparently may be the case with the barbiturates (22). The same factor may also explain the previous observation that oxygen utilization is depressed in the intact brain but not in the isolated, “resting” ganglion. This factor is difficult to evaluate, particularly from the point of view of in vitro studies.

With few exceptions (25), studies on isolated neural tissues have revealed no qualitative differences in metabolic pattern from one part to another. Instead, a metabolic gradient exists, with the rate greatest anteriorly, decreasing caudalward. Likewise, no qualitative differences have been observed in the actions of anesthetics on the various parts of the nervous system. Rather, a gradient exists for this action parallel to the metabolic rate and to the sensitivity to anoxia. This consideration returns us directly to the original problem. Although the parallel exists between resistance to anesthesia and to anoxia, and although direction of the gradient is close to the sequence of depres-
sion seen clinically, no explanation is yet at hand for the existence of the gradient.

One further suggestion on the specificity of anesthetic action deserves consideration. Synaptic transmission is known to be depressed by anesthetic action (18). As pointed out earlier, this effect may take place before any significant change occurs in over-all metabolism. Blocking of transmission may then be responsible for depressing those structures particularly whose function depends upon a greater number of relays. Such an effect has been suggested (1) to explain the inhibition of reticular formation activity. Further studies are indicated to test this hypothesis of synaptic depression and to elucidate its mechanism.

I have tried to indicate in this sketchy review how one may approach an understanding of anesthetic action from the point of view of nervous system physiology. Perhaps it is helpful to consider the whole phenomenon in terms of environmental changes. On the one hand the anesthetic agents alter the internal environment of the cells, and in so doing affect their function. The resulting disturbances in turn alter the ability of the nervous system to adjust the body to its external environment. In the latter regard, steps have been made, as in the case of reticular formation activity, to adduce concrete evidence correlating behavioral effects with localization of activity. Progress along this line has been and will continue to be made by the utilization of methods that record the electrical activity of the brain as an index of its function. The concept of levels of control in the central nervous system has been helpful in understanding anesthesia. It can continue to be useful provided its limitations as an analogy are realized.

We can look forward to advances in the understanding of the cellular actions of anesthetics. Perhaps the answer to the problem of localization of activity will be resolved in terms of specific metabolic difference among the several tissues. On the other hand, it may be more closely related to depression of synaptic transmission and the relative importance of this effect in various neural structures. We have not mentioned the possibility that the specificities of action may be related to such factors as differences in regional blood supplies, or variation in connective tissue or other barriers, which might alter the rate at which the agent is transported to or removed from the cells. These factors must not be lost sight of.

Many things are known about the actions of anesthetics on cells; many things are known about the behavioral effects. It remains to elaborate both approaches with the hope of ultimately correlating them for a complete understanding of anesthesia. In concluding, I wish to quote Gerard's words on the occasion of the Ether Centenary Celebration (20). "This progress of understanding has become more
rapid in recent decades and will undoubtedly continue to increase at an accelerating rate. Yet I venture the guess that at the next century... there will still be plenty of problems deserving discussion on the nature of anesthetic action."

SUMMARY

Recent work by French, Verzeano and Magoun on the relation of the reticular activating system to the anesthetic state has been reviewed and correlated with other facts into a scheme for understanding the behavioral aspects of anesthesia. The problem of specificity of action of anesthetics on neural structures is considered, and the conclusion is reached that present knowledge is inadequate to answer this problem. Investigations on both the behavioral and cellular levels must be continued to elucidate more fully the neural mechanisms of anesthesia.

REFERENCES

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The Annual meeting of the New England Society of Anesthetists originally announced for April 2, 1954, has been changed to April 9.